GASTROENTEROLOGY 2005;128:620–626

CLINICAL–LIVER, PANCREAS, AND BILIARY TRACT

Risk Factors of Intrahepatic Cholangiocarcinoma in the United States: A Case-Control Study

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Background & Aims: **The incidence of intrahepatic cholangiocarcinoma has been recently increasing in the United States. In this case-control study, we used the Surveillance, Epidemiology, and End Results–Medicare database to evaluate the prevalence of known risk factors for intrahepatic cholangiocarcinoma and explore other potential risk factors.** ***Methods:*** **We identified all patients with intrahepatic cholangiocarcinoma aged 65 years and older diagnosed between 1993 and 1999 in the population-based Surveillance, Epidemiology, and End Results registries (14% of the US population). Controls were randomly chosen from individuals without any cancer diagnosis in the underlying population of the Surveillance, Epidemiology, and End Results regions. We obtained information on risk factors from Medicare claims (parts A and B) for all cases and controls with at least 2 years of continuous Medicare enrollment. Unadjusted and adjusted odds ratios were calculated in logistic regression analysis.** ***Results:*** **A total of 625 cases and 90,834 controls satisfied the inclusion and exclusion criteria. Cases were older than controls (78.7 vs. 76.5 years; $P = .02$) and were more likely to be male (48.3% vs. 36.8%; $P < .0001$). The racial composition was similar between cases and controls. Several risk factors were significantly more prevalent among cases. These included nonspecific cirrhosis (adjusted odds ratio, 27.2; $P < .0001$), alcoholic liver disease (adjusted odds ratio, 7.4; $P < .0001$), hepatitis C virus infection (adjusted odds ratio, 6.1; $P < .0001$), human immunodeficiency virus infection (adjusted odds ratio, 5.9; $P = .003$), diabetes (adjusted odds ratio, 2.0; $P < .0001$), and inflammatory bowel diseases (adjusted odds ratio, 2.3; $P = .002$).** ***Conclusions:*** **This population-based study shows that in addition to previously well described risk factors, several others could be associated with intrahepatic cholangiocarcinoma. These include hepatitis C virus, human immunodeficiency virus, liver cirrhosis, and diabetes.**

In the United States, an estimated 17,550 primary liver cancers will be diagnosed in 2005.[1] Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER) indicate that approximately 15% of these will be intrahepatic cholangiocarcinomas (ICC), the second most common primary liver tumor (after hepatocellular carcinoma). Studies using the SEER data have shown a marked increase in the incidence of ICC in the United States.[2,3] Most of this increase occurred after 1985, and it seems to be a true increase rather than an artifact of better detection or reclassification.[3] The reasons behind this increasing incidence are not clear, however, because the epidemiology of ICC is poorly understood in low-risk areas such as the United States. In these areas, ICC is known to be associated with disorders of the biliary tract, especially primary sclerosing cholangitis, and with inflammatory bowel diseases.[4] Whether the incidence of these conditions has changed is unclear. ICC among primary sclerosing cholangitis patients is most commonly diagnosed at a relatively young age (47 years in one study[5]), but the recent increase was noted to affect mostly older people.[3]

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, as well as liver cirrhosis, regardless of etiology, have been examined as potential risk factors for ICC in countries other than the United States.[6–9] Given the high prevalence of HCV infection acquired during the 1960s and 1970s, it is conceivable that the increase in ICC incidence might be related to HCV infection.[10] In addition, several studies have suggested that diabetes

Abbreviations used in this paper: HIV, human immunodeficiency virus; HMO, health maintenance organization; ICC, intrahepatic cholangiocarcinoma; ICD, International Classification of Diseases; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results.

0016-5085/05/$30.00
doi:10.1053/j.gastro.2004.12.048

mellitus also increases the risk of primary liver cancer: both hepatocellular carcinoma and ICC.[11,12] No studies conducted in the United States, however, have evaluated the role of HCV, HBV, diabetes, or chronic liver diseases with ICC. We therefore conducted this study to examine these potential associations and to explore other possible risk factors.

Materials and Methods

Data Source

Data used for this study were obtained from the SEER–Medicare database, which is the linkage of SEER registry information with Medicare claims data. The SEER program is an ongoing contract-supported program of the National Cancer Institute to collect population-based cancer incidence and survival data. The SEER program has included, since 1992, population-based cancer registries in 5 states and 6 metropolitan areas that represent approximately 14% of the US population.[13] These registries include the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and 6 metropolitan areas: Los Angeles, San Francisco/Oakland, San Jose, Detroit, Seattle, and Atlanta. For each case identified, the SEER program collects demographic features, as well as information on the date of cancer diagnosis, cancer site, and histology. The International Classification of Diseases (ICD) for Oncology version 2 is used by SEER to classify the primary tumor site and histological type for all cancers ascertained by the program.[14]

Medicare claims data are collected for both Medicare part A and part B benefits. Medicare is the primary health insurer for approximately 97% of individuals aged 65 years and older in the United States. Persons younger than 65 years of age can be eligible for Medicare benefits because of disability or end-stage renal disease. However, these patients are significantly different from patients aged 65 years and older with regard to demographic features and clinical characteristics. Approximately 95% of Medicare beneficiaries are covered by both part A and part B benefits.[13] Medicare claims data for all part B–covered benefits include outpatient hospital services and physician office visits. These files contain dates of services, as well as both ICD 9th revision, clinical modification (ICD-9-CM) diagnosis codes and Current Procedural Terminology version 4 codes for all billed claims.[13]

The linkage of SEER–Medicare data is a collaborative effort by the National Cancer Institute, the SEER registries, and Centers for Medicare and Medicaid Services.[13] This database contains Medicare part A and part B claims data for all patients identified by SEER registries between 1973 and 1999, although Medicare claims are available only beginning in 1991. To link patients identified by the SEER registries to information contained in the Medicare claims files, the SEER and Medicare Enrollment Databases are merged by using an algorithm that matches on social security number, name, sex, and date of birth. Using this method to perform the linkage captures approximately 93% of patients in the SEER database aged 65 years and older. Additional details regarding this linkage have been described previously.[13]

Study Population

Cases. All patients aged 65 years and older diagnosed with ICC in SEER registries who were also enrolled in Medicare between 1993 and 1999 were eligible for inclusion. Eligibility was limited to persons diagnosed no earlier than 1993 and who had 2 years of Medicare data before the date of diagnosis. Only patients with diagnostic confirmation of ICC (ICD for Oncology histology codes 8160, 8162, 8260, 8481, 8500, and 8560) were included in our analysis. Diagnostic confirmation was defined as having positive histology, cytology, laboratory test/marker study, direct visualization, or positive radiology tests. Patients with clinical diagnoses only or an unknown method of confirmation were excluded. In addition, we excluded patients diagnosed with stomach, colon, lung, pancreatic, breast, or rectal cancers within the 5 years before the date of ICC diagnosis to further ensure the inclusion of only ICC, rather than metastatic liver cancers.

Controls. The controls included in the study were derived from the 5% random sample of Medicare-enrolled beneficiaries with no cancer of any type residing in the geographic regions of SEER registries. These are noncancer controls that are linked to the SEER–Medicare data. The same inclusion/exclusion criteria used in case selection were applied to controls.

To include cases and controls with equal exposure to risk factor information, we selected only patients with continuous enrollment in Medicare parts A and B for at least the 2 years before and up to 1 year after ICC diagnosis or until death. Cases and controls were matched on the years of search for risk factors to minimize the possibility of differing testing and diagnosis trends. We excluded patients enrolled in a health maintenance organization (HMO) during this time frame because Medicare HMO plans have historically not been required to submit individual claims to Centers for Medicare and Medicaid Services for specific services received by patients enrolled in Medicare.[13] Patients whose ICC diagnoses were reported exclusively by death certificates or at autopsy were also excluded.

We studied several potential risk factors for ICC belonging to 4 broad categories: bile duct diseases, infectious etiologies, chronic noninfectious liver diseases, and 1 group of miscellaneous potential risk factors. Bile duct diseases included liver flukes (ICD-9 codes 121.1, 121.0, 121.3), nonsuppurative cholangitis (ICD-9 code 571.6), cholangitis (ICD-9 codes 575.8 and 576.1), choledocholithiasis (ICD-9 code 574.5), choledochal cysts (ICD-9 code 751.69), cholestasis (ICD-9 code 576.8), biliary cirrhosis (ICD-9 code 571.6), and anomalous bile duct (ICD-9 code 751.60). Primary sclerosing cholangitis does not have an ICD code separate from that of cholangitis (ICD-9 codes 575.8 and 576.1), so it could not be examined outside that grouping. The infectious diseases group included human immunodeficiency virus (HIV) infection

(ICD-9 codes 042–044), HBV infection (ICD-9 codes 070.22, 070.23, 070.32, 070.33, and V02.61), and HCV infection. HCV was defined by using ICD-9 codes for HCV (ICD-9 codes 070.41, 070.44, 070.51, 070.54, and V02.62) or for unspecified hepatitis (ICD-9 codes 070.9, 571.4, 571.8, and 571.9). Before 1992, no ICD-9 code was available to indicate a diagnosis of HCV; thus, we assumed that all patients with HCV were classified as having unspecified hepatitis. Chronic noninfectious liver diseases included hemochromatosis (ICD-9 code 275.0), alcoholic liver disease, and nonspecific cirrhosis. Alcoholic liver disease was defined by the presence of ICD-9 codes for alcoholic fatty liver disease (ICD-9 code 571.0), alcoholic hepatitis (ICD-9 code 571.1), alcoholic cirrhosis of the liver (ICD-9 code 571.2), alcoholic liver damage (ICD-9 code 571.3), and cirrhosis (ICD-9 codes 571.5 and 571.6) in the presence of alcoholism (ICD-9 codes 291, 303, and 305.0). Nonspecific cirrhosis was defined by the presence of cirrhosis (ICD-9 codes 571.5 and 571.6) without the presence of HCV, HBV, or alcoholic liver disease. Finally, we examined type 2 diabetes mellitus (ICD-9 code 250), smoking (ICD-9 code V15.82), and inflammatory bowel diseases (IBD). IBD included ulcerative colitis (ICD-9 codes 556, 556.9, 556.1, 556.2, 556.3, 556.5, 556.6, and 557.0) and Crohn's disease (ICD-9 code 555).

Risk factors were identified on the basis of Medicare part A or B claims for the 3 years preceding and 2 years succeeding the index date (or until death), with the exception of diabetes. To minimize detection bias that might be introduced secondary to excessive workup and diagnosis of patients with liver cancer, we excluded all risk factor diagnoses made in the 1 year preceding cancer diagnosis.

Other Collected Information

Covariates included age, race, geographic region, and state buy-in status. Race was classified as white, black, Hispanic, Asian, and other. Geographic region was categorized according to the 11 SEER registries (Utah, Atlanta, Connecticut, Detroit, Hawaii, Iowa, Los Angeles, New Mexico, San Francisco, San Jose, and Seattle). The state buy-in variable in Medicare indicates whether a third-party payer, most frequently Medicaid or a Medicaid-based Medicare supplemental program, was paying for a beneficiary's Medicare premiums. These individuals were considered Medicare/Medicaid dually enrolled, and this served as a proxy for poor socioeconomic status.

Statistical Analysis

We compared the demographic features and prevalence of risk factors associated with ICC between patients diagnosed with ICC and controls. Chi-square tests were used for categorical variables, and t tests were used for continuous variables. Unadjusted odds ratios (ORs) and 95% confidence intervals (CIs), as well as P values, were calculated for each risk factor.

Logistic regression analysis was used to examine the association between each ICC diagnosis and each risk factor, adjusting for age, sex, race, geographic region, and Medicare/Medicaid dual enrollment. Wald χ^2 tests were used to determine the significance of each variable. Adjusted ORs and 95% CIs were calculated for each parameter estimate.

Table 1. Comparison of Demographic Features Between Patients With Intrahepatic Cholangiocarcinoma and Controls Without any Cancer Identified Between 1993 and 1999 in SEER-Medicare

	ICC cases (N = 625)	Controls (N = 90,834)	*P* value
Mean age (SD)	78.7 (6.4)	76.5 (6.9)	.02
Gender			
Women	302 (48.3%)	33,400 (36.8%)	<.0001
Men	323 (51.7%)	57,434 (63.2%)	
Race			
White	505 (80.8%)	74,583 (81.4%)	.02
Black	32 (5.1%)	6547 (6.8%)	
Hispanic	13 (2.1%)	2673 (2.8%)	
Asian	37 (5.9%)	4918 (5.1%)	
Other	38 (6.1%)	3835 (4.0%)	
Geographic location			
Atlanta	35 (5.6%)	5572 (6.1%)	.04
Utah	22 (3.5%)	4318 (4.8%)	
Connecticut	88 (14.1%)	11,849 (13.0%)	
Detroit	82 (13.1%)	13,557 (14.9%)	
Hawaii	22 (3.5%)	2646 (2.9%)	
Iowa	91 (14.6%)	11,829 (13.0%)	
Los Angeles	107 (17.1%)	16,145 (17.8%)	
New Mexico	16 (2.6%)	4681 (5.2%)	
San Francisco	62 (9.9%)	7317 (8.1%)	
San Jose	28 (4.5%)	4183 (4.6%)	
Seattle	72 (11.5%)	8737 (9.6%)	
Medicare/medicaid dual enrollment	116 (18.6%)	13,148 (14.5%)	<.0001

Results

We initially identified 1224 patients with ICC diagnostically confirmed between 1993 and 1999 and who were 65 years or older. Of these cases, 625 patients with ICC were included in the study cohort. The possibility of missing risk factor information led to the exclusion of 574 cases (250 were enrolled in a Medicare HMO plan during the 2 years before or after the date of ICC diagnosis, 313 were enrolled in Medicare part A and part B for less than 2 years before the index date, and 11 were reported solely by autopsy or death certificate), and 25 were excluded for the possibility of misdiagnosis because of the presence of stomach, colon, lung, pancreatic, breast, or rectal cancer within the 5-year period before the date of ICC diagnosis.

The control group consisted of 90,834 individuals without ICC or any other cancer that satisfied the inclusion criteria listed previously. Table 1 summarizes the demographic features and characteristics of cases and controls. The mean age of cases was higher than that of controls (78.7 vs. 76.5 years; $P = .02$). There were also

Table 2. Comparison of the Prevalence of Risk Factors Between Intrahepatic Cholangiocarcinoma (ICC) Cases and Noncancer Controls

	ICC cases (N = 625)		Controls (N = 90,834)		
	N	%	N	%	*P* value
Chronic noninfectious liver disease					
Nonspecific cirrhosis	53	8.5	325	0.4	<.0001
Alcoholic liver disease	14	2.2	282	0.3	<.0001
Infectious					
HCV-specific codes	5	0.8	161	0.2	.006
HCV (including unspecified hepatitis)	35	5.6	940	1.0	<.0001
Bile duct disease					
Cholangitis	12	3.4	279	0.2	<.0001
Choledocolithiasis	7	1.1	351	0.3	.002
Cholestasis	5	0.8	161	0.1	<.0001
Other risk factors					
Smoking	24	3.8	1927	2.1	.003
Diabetes	165	26.4	14,201	15.6	<.0001
IBD	15	2.4	997	1.1	.002

more men among ICC cases compared with controls (48.3% vs. 36.8%; $P < .0001$). The race distribution showed a higher prevalence of Asians and people of other ethnic backgrounds in the ICC group ($P = .02$). Similarly, Medicare/Medicaid dual enrollment was higher among ICC cases (18.6% vs. 14.5%; $P < .0001$). Although these differences in the demographic features were statistically significant, most of the differences are of little clinical significance.

Risk Factors

Risk factors were classified into 4 main categories. The distributions of risk factors in each of the categories are summarized in Table 2.

1. Chronic liver diseases of noninfectious etiology: nonspecific cirrhosis and alcoholic liver diseases were more prevalent among ICC cases than among controls ($P < .0001$; Table 2). Hemochromatosis was the only risk factor that was not significantly higher among cases (0.3% vs. 0.3%, $P = .7$).
2. Infectious etiologies: both HIV and HCV infection were more prevalent among ICC cases than among controls. The prevalence of HIV infection was 0.5% among ICC cases and 0.1% among controls ($P = .02$). Among ICC cases, the prevalence of HCV infection was 0.8% and increased to 5.6% if persons with unspecified hepatitis were included. This proportion was significantly higher than HCV prevalence among controls (0.2%) and was 1.0% when unspecified hepatitis was included ($P < .0001$). The prevalence of HBV infection, however, was similar in both cases and controls (0.2% and 0.2%).
3. Bile duct diseases: compared with controls, ICC cases were more likely to have a diagnosis of cholangitis (1.9% vs. 0.2%; $P < .0001$), choledocholithiasis (1.1% vs. 0.3%; $P = .002$), and cholestasis (0.8% vs. 0.1%; $P < .0001$), but not abnormal bile duct anatomy (0.2% vs. 0%, $P = .3$).
4. Other risk factors: other risk factors studied included IBD, smoking, and diabetes. Among ICC cases, 3.8% were smokers, compared with 2.1% in controls ($P = .003$). Likewise, the prevalence of diabetes was higher among cases when compared with controls (26.4% vs. 15.6%; $P < .0001$), as was the prevalence of IBD (2.4% vs. 1.1%; $P = .002$).

Logistic Regression Analysis

Using a logistic regression model that adjusted for demographics (age, sex, and race), geographic location, and Medicare/Medicaid dual enrollment status, we calculated adjusted ORs for the different risk factors. This analysis showed that, after adjustment, all the risk factors that were significant in the univariate analyses remained statistically significant in the multivariate analysis (Table 3). ICC cases were more likely to have evidence of chronic liver disease when compared with controls. For example, the presence of nonspecific cirrhosis was strongly associated with ICC (adjusted OR, 27.2; 95% CI, 19.9–37.1). Similarly, HCV and HIV infections, but not HBV infection, were strongly associated with ICC (Table 3). ICC cases were almost 6 times more likely to have HCV infection than controls (OR, 6.1; 95% CI, 4.3–8.6). Even if only patients with specific HCV infection codes were included (ie, if those with codes of unspecified hepatitis were excluded), the associ-

Table 3. Multiple Logistic Regression Analysis Examining the Association Between Each Risk Factor and Intrahepatic Cholangiocarcinoma While Adjusting for Age, Gender, Race, Geographic Location, and Medicare/Medicaid Dual Enrollment

	Adjusted odds ratio	95% Confidence intervals	*P* value
Chronic noninfectious liver disease			
Nonspecific cirrhosis	27.2	19.9–37.1	<.0001
Alcoholic liver disease	7.4	4.3–12.8	<.0001
Hemochromatosis	1.1	0.3–4.3	.9
Infectious			
HBV	0.8	0.1–5.9	.8
HIV	5.9	1.8–18.8	.003
HCV-specific codes	5.2	2.1–12.8	<.0001
HCV (including unspecified hepatitis)	6.1	4.3–8.6	<.0001
Bile duct disease			
Cholangitis	8.8	4.9–16.0	<.0001
Choledocolethiasis	4.0	1.9–8.5	.0004
Cholestasis	6.7	2.7–21.6	<.0001
Abnormal bile duct anatomy	3.0	0.4–21.6	.3
Other risk factors			
Smoking	1.8	1.2–2.70	.007
Diabetes	2.0	1.6–2.4	<.0001
IBD	2.3	1.4–3.8	.002

ation with ICC remained strong (OR, 5.2; 95% CI, 2.1–12.8).

The logistic regression analysis also confirmed the strong association between bile duct diseases and ICC. Cholangitis, choledocholithiasis, and cholestasis, but not abnormal bile anatomy, were all strongly associated with ICC. For example, subjects with ICC were almost 7 times more likely to have cholestasis for at least 2 months before cancer diagnosis than were controls (adjusted OR, 6.7; 95% CI, 0.4–21.6). Similarly, ICC was strongly associated with smoking, diabetes, and IBD in the multivariate model (Table 3). Separating IBD into ulcerative colitis and Crohn's disease showed that the association with ICC was significant for ulcerative colitis (OR, 2.2; 95% CI, 1.2–3.9) but not for Crohn's disease (OR, 2.0; 95% CI, 0.6–6.3). ICC cases were twice as likely to have diabetes diagnosed at least 1 year before cancer diagnosis when compared with controls (adjusted OR, 2.0; 95% CI, 1.6–2.4).

We also constructed several models that examined the association between ICC and HCV and adjusted for 1 additional diagnosis at a time (namely, nonspecific cirrhosis, HCV, HIV, and diabetes). There was no significant change in the direction or the magnitude of the observed association between HCV and ICC in any of these models.

Considering that diagnostic confirmation might be low among cases diagnosed by marker or radiology study alone, we repeated the analysis and included only cases with very strong diagnostic confirmation (ie, positive histology or cytology). Sixty-four percent (399 cases) had tissue confirmation. The repeat analysis showed that all of the previously described associations persisted (data not shown).

A comparison of ICC cases that had known risk factors with those that had no known risk factor found that the sex and race distributions were similar in both groups. However, the mean age of cases with no known risk factor was significantly higher than the mean age of subjects with defined risk factors (79.6 vs. 78.1 years; $P = .003$). Iowa, New Mexico, Hawaii, and San Jose tended to have more subjects with idiopathic disease than Connecticut, Detroit, and Los Angeles. Cases with known risk factors were also more likely to have Medicare/Medicaid dual enrollment when compared with cases that had no known risk factor (21.5% vs. 14.0; $P = .02$).

Discussion

This is the largest US population–based case-control study to examine risk factors for ICC. The findings suggest that HCV infection, but not HBV infection, is a potentially strong risk factor for ICC. In addition, the presence of chronic and advanced liver disease of any etiology, HIV infection, diabetes, and smoking were significant risk factors for ICC.

An important indicator of the external validity of our study is that it confirms the association between ICC and previously described risk factors, including cholangitis and choledocholithiasis. Similarly, a history of IBD—specifically, ulcerative colitis disease—was also strongly associated with ICC.

Chronic liver diseases due to nonviral etiology, especially in the presence of cirrhosis, are strongly associated with ICC. ICC cases had a higher prevalence of alcoholic liver disease, nonalcoholic cirrhosis, and complications of liver disease. These findings suggest that chronic and end-stage liver diseases are important risk factors for ICC; this is similar to what is noted in hepatocellular carcinoma. Those findings are similar to findings in studies from other countries.[6–9] For example, a Danish cohort study that examined 11,605 persons with cirrhosis for an average follow-up of approximately 6 years found a significant 10-fold increased risk for ICC among patients with cirrhosis of any cause when compared with the general population.[9]

HCV, but not HBV, infection was strongly associated with ICC risk. At least 3 studies have previously shown

a positive association between ICC and at least 1 type of viral hepatitis.[6–8] The first was a case-control study from Korea that compared 41 cases of ICC with 406 controls and found that 13.8% and 12.5% of cases and 3.5% and 2.3% of controls were HCV and HBV positive, respectively.[8] The second study was a prospective cohort study from Japan that showed a relatively high incidence of ICC among patients with HCV-related cirrhosis.[7] In that study, the investigators reported that 14 of 600 (2.3%) patients with HCV-related cirrhosis developed ICC during an average follow-up of 7.2 years. Similarly, a third study, which was an Italian case-control study (21 cases and 686 controls), found a positive association between HCV and HBV infections and ICC.[6] According to this study, the prevalence of HCV and HBV in cases was 23.1% and 11.5%, respectively, as compared with 6.1% and 5.5% in controls. In summary, increasing evidence implicates viral hepatitis—especially HCV—as a risk factor for ICC. In our cohort, it is possible that the number of HBV cases was too small to detect any differences between cases and controls. HCV might play a direct role in the pathogenesis of ICC. One study has detected HCV RNA in cholangiocarcinoma tissue, a finding that supports the potential role of HCV infection in the pathogenesis of ICC.[15] In addition, HCV has been shown to cause bile duct epithelial cell injury, which can lead to a range of proliferative, inflammatory, and degenerative changes.[16]

In addition to the association with HCV, our study found an association between ICC and HIV infection. HIV is known to be associated with cholangitis either directly (acquired immunodeficiency syndrome cholangiopathy) or via other opportunistic infections (eg, cytomegalovirus).[17,18] It is possible that HIV-related cholangitis leads to changes similar to those induced by other inflammatory conditions of the bile duct that eventually result in cancer. It is also possible, of course, that HIV only seems to be associated with ICC because HIV infection tends to co-occur with HCV infections. Further study of HIV, HCV, and ICC will be required to elucidate the relationship of the viruses to ICC.

In addition to the previously mentioned risk factors, smoking and diabetes were more prevalent among ICC cases as compared with controls in our cohort. Smoking is a known risk factor for a number of malignancies, and it has been suggested to be a risk factor for ICC among sclerosing cholangitis patients[19] but has not been previously reported as an independent risk factor for ICC. The prevalence of smoking in our cohort was lower than expected and was likely undermeasured, because the smoking status of all participants was not systematically verified. Similarly, this is the first study to report an association between diabetes and ICC. A previous cohort study reported an association between diabetes and primary liver cancer in Denmark.[11] Although cholangiocarcinomas were included among the primary liver cancers reported, it was not clear whether ICC, by itself, was significantly associated with diabetes. It has to be kept in mind, however, that diabetes could be a complication of chronic liver disease. Diabetes is clearly more easily diagnosed than liver diseases and might be a surrogate for these diseases. To minimize the effect of this association, we included only diabetes diagnoses that were made at least 1 year before cancer diagnosis. Even with this exclusion, the association remained strong. Whether diabetes itself or other associated conditions, such as obesity or hyperlipidemia, are the true risk factors for ICC is not clear, and this study is not suitable to examine this hypothesis.

In addition to identifying new risk factors and confirming established ones, our study suggests that a substantial proportion of ICC cases (38.9%) have no identifiable risk factors. The significant differences in geographic location between subjects with known risk factors and those with no identifiable risk factors might reflect regional differences in the workup of ICC patients. The high percentage of subjects with unidentified risk factors underscores the need for more studies that explore and identify those risk factors.

Although our study was large and encompassed individuals of all ethnicities, it had several potential limitations. First, we used health-care claims as the source for risk factor information, and the accuracy and completeness of the information is not known. However, we took several steps to increase the possibility of complete capture of risk factor information. We restricted the study cohort to individuals with at least 2 years of continuous Medicare part A and part B enrollment and no enrollment in an HMO plan. In these patients, Medicare files capture 100% of claims for tests, procedures, outpatient visits, and hospitalization for these individuals.[13] In addition, we included only diagnoses that were made at least 1 year before cancer diagnosis, hence minimizing diagnosis bias that might be associated with extensive workup of cancer cases.

Another potential limitation is the generalizability of the results obtained among patients aged 65 years and older to the entire US population. It should be noted, however, that 71% of ICC in the United States is diagnosed among persons in this age group, so the Medicare population represents the high-risk group.[18] Finally, there is the possibility of diagnostic bias in which cases with cancer are more likely than controls to undergo testing and thus have more diagnoses in general than

controls. In the case of a biliary tumor such as ICC, individuals would be more likely to be tested for hepatitis viruses than would other individuals. As a consequence, our findings concerning HCV should be interpreted cautiously. To minimize the effect of diagnosis bias, we applied strict criteria in selecting diagnoses to be included in our analysis (excluding all diagnoses made in the year preceding cancer diagnosis). This, however, does not completely eliminate the possibility of residual diagnosis bias. In addition, the small numbers of certain diagnoses (for example HIV, HBV, and hemochromatosis) among cases makes it difficult to make any strong conclusions regarding the described associations.

Important strengths of this study are related to its data source, as well as case and control definitions. The SEER–Medicare database is population based, and the registries are selected to represent the entire US population; therefore, our overall findings are probably generalizable to the entire US population aged 65 years and older.[13] The SEER program maintains at least a 98% completeness rate for case ascertainment.[13] An additional strength is the availability of a large number of controls that were obtained from a randomly chosen sample of individuals without cancer who resided in the same area covered by the SEER registries during the time in which ICC cases were diagnosed. Finally, all cases of ICC included in this analysis were confirmed by pathology, radiology, laboratory testing, or a combination of these.

In conclusion, our results suggest several new risk factors for ICC in the United States. These include hepatitis C, chronic liver disease of any etiology, HIV infection, diabetes, and smoking. Future studies are needed to further explore the role of these risk factors.

References

1. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ. Cancer statistics, 2005. CA Cancer J Clin 2005;55:10–30.
2. Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 2001;33: 1353–1357.
3. Shaib YH, Davila JA, McGlynn K, El-Serag HB. Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase? J Hepatol 2004;40:472–477.
4. de Groen PC, Gores GJ, LaRusso NF, Gunderson LL, Nagorney DM. Biliary tract cancers. N Engl J Med 1999;341:1368–1378.
5. Chalasani N, Baluyut A, Ismail A, Zaman A, Sood G, Ghalib R, et al. Cholangiocarcinoma in patients with primary sclerosing cholangitis: a multicenter case-control study. Hepatology 2000;31:7–11.
6. Donato F, Gelatti U, Tagger A, Favret M, Ribero ML, Callea F, et al. Intrahepatic cholangiocarcinoma and hepatitis C and B virus infection, alcohol intake, and hepatolithiasis: a case-control study in Italy. Cancer Causes Control 2001;12:959–964.
7. Kobayashi M, Ikeda K, Saitoh S, Suzuki F, Tsubota A, Suzuki Y, et al. Incidence of primary cholangiocellular carcinoma of the liver in Japanese patients with hepatitis C virus-related cirrhosis. Cancer 2000; 88:2471–2477.
8. Shin HR, Lee CU, Park HJ, Seol SY, Chung JM, Choi HC, et al. Hepatitis B and C virus, *Clonorchis sinensis* for the risk of liver cancer: a case-control study in Pusan, Korea. Int J Epidemiol 1996;25:933–940.
9. Sorensen HT, Friis S, Olsen JH, Thulstrup AM, Mellemkjaer L, Linet M, et al. Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. Hepatology 1998;28:921–925.
10. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, Kaslow RA, Margolis HS. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999;341:556–562.
11. Wideroff L, Gridley G, Mellemkjaer L, Chow WH, Linet M, Keehn S, Borch-Johnson K, Olsen JH. Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. J Natl Cancer Inst 1997;89:1360–1365.
12. Adami HO, Chow WH, Nyren O, Berne C, Linet MS, Ekbom A, Wolk A, McLaughlin JK, Fraumeni JF. Excess risk of primary liver cancer in patients with diabetes mellitus. J Natl Cancer Inst 1996;88:1472–1477.
13. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care 2002;40(8 Suppl):3–18.
14. The SEER program code manual. 3rd ed. Bethesda MD: National Cancer Institute, 1998.
15. Yin F, Chen B. Detection of hepatitis C virus RNA sequences in hepatic portal cholangiocarcinoma tissue by reverse transcription polymerase chain reaction. Chin Med J (Engl) 1998;111:1068–1070.
16. Ahrendt SA, Nakeeb A, Pitt HA. Cholangiocarcinoma. Clin Liver Dis 2001;5:191–218.
17. Wilcox CM, Monkemuller KE. Hepatobiliary diseases in patients with AIDS: focus on AIDS cholangiopathy and gallbladder disease. Dig Dis 1998;16:205–213.
18. Chui DW, Owen RL. AIDS and the gut. J Gastroenterol Hepatol 1994;9:291–303.
19. Bergquist A, Glaumann H, Persson B, Broome U. Risk factors and clinical presentation of hepatobiliary carcinoma in patients with primary sclerosing cholangitis: a case-control study. Hepatology 1998;27:311–316.

Received May 21, 2004. Accepted November 17, 2004.

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